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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,551	03/30/2006	Isaiah J. Fidler	UTSC:767US	3754

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/26/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,551	FIDLER ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *23-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/09/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I (Claims 1-22), without traverse in the reply filed on November 20, 2006 is acknowledged.

2. Claims 1-42 are pending.

Claims 23-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 20, 2006.

Claims 1-22 are under examination.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/420,209, filed 10/22/2002, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claims 5 and 6 do not have support for priority under application 60/420,209. These claims are supported under Application No. 60/453,330, filed 3/10/2003.

Therefore, Claims 1-4 and 7-22 receive the priority date of 10/22/2002 and Claims 5 and 6 receive the priority date of 3/10/2003.

Specification

4. The disclosure is objected to because of the following informalities: There are minor grammatical errors in the specification which make certain sections unclear. For example, on page 7 line 5 the sentence reads "Body weight of each mouse was measured once for 6 weeks." It is unclear if this means once during the 6-week period or more frequently during the 6-week period.

Appropriate correction is required throughout.

5. The use of the trademarks Taxol™ and Navelbine™ have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Trademark symbols for the above noted trademarks are not included in the application. Appropriate correction is required throughout.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a mouse with occult metastatic melanoma by administering a composition comprising an immunomodulatory peptide and a baculovirus-insect cell preparation in combination with a tumor antigen or a second cancer therapy of radiotherapy, chemotherapy, or surgery, does not reasonably provide enablement for treating a primary tumor of bone, liver, spleen, pancreas, lung, colon, testis, ovary, breast, cervix, prostate, or uterine cancer that has metastasized to brain or treating the subject with occult metastasis with an inflammatory stimulus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of treating a subject with occult brain metastasis by administering a composition comprising an immunomodulatory peptide and a baculovirus-insect cell preparation including an immunomodulatory polypeptide of IFN-α, IFN-β, IFN-γ, IL-1, IL-2, IL-6, IL-7, IL-12, IL-15, IL-16, or GM-CSF, an inflammatory stimulus of bacteria, endotoxin, or unmethylated DNA, and a tumor antigen of MAGE-1, MAGE-3, Melan-A, P198, P1A, gp100, TAG-72, $p185^{HER2}$, milk mucin core protein, carcinoembryonic antigen (CEA), P91A, p53, $p21^{ras}$, P210, BTA, or tyrosinase expressed from a recombinant baculovirus vector wherein the composition comprises *Spodoptera* or *Trichoplusia* cells, is administered in two or three doses, comprises between about 10^5 and 10^7 insect cells, wherein the insect cells are intact or disrupted, the composition is lyophilized or freeze thawed, wherein the treatment is a second anti-cancer therapy and the subject is a human subject who had previously received cancer therapy.

The specification enables treatment of metastasis in a mouse model with an immunomodulatory polypeptide in a baculovirus-insect cell preparation.

The specification does not enable the composition further comprising an inflammatory stimulus. The specification does not enable the treatment of metastasis derived from bone, liver, spleen, pancreas, lung, colon, testis, ovary, breast, cervix,

prostate or uterus. The specification does not enable the composition as a second therapy. The specification does not enable the treatment of a human subject with occult brain metastasis.

Claims 1, 5, and 6 recite a method for treating a subject with occult brain metastasis comprising administering a composition comprising an immunomodulatory polypeptide and a baculovirus-insect cell preparation wherein the composition further comprises an inflammatory stimulus of whole bacteria, endotoxin, or unmethylated DNA.

Ozawa, et al. (International Journal of Oncology 2003, Vol. 22 pages 977-984) teach administering a baculovirus-insect cell preparation to treat occult liver metastasis. Ozawa, et al. teach that insect cell DNA contains unmethylated CpG DNA motifs, which can augment T cell responses to specific antigen and that type I interferons may mediate stimulation of T-cells by CpG DNA. Ozawa, et al. also teach intra-tumoral injection of a baculoviral vector expressing GM-CSF (thus containing a CpG DNA inflammatory stimulus) had minimal therapeutic effects (page 982 2nd column, 1st full paragraph).

Claims 1 and 19 recite a method for treating a subject with occult brain metastasis comprising administering a composition comprising an immunomodulatory polypeptide and a baculovirus-insect cell preparation wherein the subject is a human subject.

Satyamoorthy, et al. (Cancer and Metastasis Reviews 1999, Vol. 18, pages 401-405) teaches a number of mouse models of human melanoma (table 1) and the lack of

context between the human skin architecture and the mouse model (abstract). Cranmer, et al. (Melanoma Research 2005, Vol. 15 No. 5, pages 325-56) teach that the rodent models of melanoma metastasis have highlighted the complex biology of cerebral metastasis. Since the specification has not provided support for the use of a baculovirus-cell preparation for treatment of occult brain metastasis in a human subject, and it is not clear if the mouse model used in the specification can be translated to human treatments and since the above mentioned references provide evidence of the unpredictability of rodent metastatic melanoma models, one of skill in the art would be required to perform undue experimentation to determine the efficacy of a baculovirus-cell preparation as a human therapy for brain metastasis.

The claims are not commensurate in scope with the enablement provided in the specification. Since the specification has not provided support for the use of a relative sample of an inflammatory stimulus, and the above mentioned references provide evidence of the unpredictability of immune stimuli as cancer therapy, one of skill in the art would be required to perform undue experimentation to determine the efficacy of a baculovirus-cell preparation as a second therapy for brain metastasis.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 3, and 4 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-6 of U.S. Patent No. 6,872,385 (Fidler, et al.) in view of Fidler, et al. (Cancer and Metastasis Reviews 1999, Vol. 18, pages 387-400).

The claims of the present application are drawn to a method of treating occult brain metastasis by administering a composition comprising an immunomodulatory polypeptide and a baculovirus insect cell preparation wherein the immunomodulatory polypeptide is IFN-β.

The claims of U.S. Patent No. 6,872,385 are drawn to a method of inhibiting cancer growth in a host having a cancer comprising isolating cancer cells from said host, rendering said cancer cells inactive, reintroducing said inactivated cancer cells into said host in a pharmaceutical composition, said pharmaceutical composition further comprising an insect cell composition and interferon β, wherein the cancer is metastatic, the composition comprises exogenous DNA in a baculovirus expression vector and encodes interferon β. The claims do not teach a treatment for occult brain metastasis. This deficiency is made up for in the teachings of Fidler, et al.

Fidler, et al. teach melanoma metastasizes to the brain (page 387 1st column) and K-1735 melanoma cells are used in a mouse model for metastasis (page 387-388, particularly page 388, last paragraph 1st column).

It would have been prima facie obvious at the time the claimed invention was made to have treated melanoma metastasis in the brain using the baculovirus composition of the Fidler patent as taught by Fidler, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the baculovirus cell composition of the Fidler patent for brain metastasis because Fidler, et al. teach that melanoma frequently metastasizes to the brain. Thus, it would have been obvious to one of ordinary skill in

the art at the time the claimed invention was made to have used the treatment method of the Fidler patent for treatment of brain metastasis.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-4, 7, 8, and 10-14 are rejected under 35 U.S.C. 103(a) as being obvious over Lu, et al. (International Journal of Cancer 2002, Vol. 100 pages 480-485) in view of Fidler, et al. (Cancer and Metastasis Reviews 1999, Vol. 18, pages 387-400).

Claims 1, 3 and 4 have been described supra.

Claims 2, 7, 8, and 10-14 are drawn to a method for treating occult metastasis by administering to a subject a composition comprising an immunomodulatory peptide and a baculovirus-insect cell preparation wherein the composition in injected directly into the tumor or into tumor vasculature not located in the brain, the composition comprises *Spodoptera* or *Trichoplusia* cells, wherein there is a second administration of the composition, and the composition comprises about 10^5 to 10^7 cells, intact cells, disrupted cells, lyophilized cells, and freeze thawed cells.

Lu et al. teaches a method for treating lung metastasis comprising administering a composition comprising a baculovirus-insect cell preparation from *Trichoplusia* cells and an immunomodulatory peptide, IFN-β (see table 1 and page 481 last paragraph to 1st paragraph page 482) in either lyophilized or frozen-thawed preparations (page 481 2nd paragraph under results) in either one or two doses (page 481 3rd paragraph under results) by injecting cells into the tumor (page 481 1st paragraph under results). Lu, et al. also teaches that each dose contained 2 units of the cell preparation wherein a unit

is defined as 10^6 H5 (derived from *Trichoplusia ni*) cells, $2x10^7$ PFU BV (Baculovirus) and $2x10^4$ units IFN-β (page 481 1st paragraph under results). Lu, et al. teach a model for subcutaneous tumors of the highly metastastic murine UV-2237m fibroscarcoma or K-1735M2 melanoma cell lines which generate spontaneous lung metastasis (page 481 1st column). Lu, et al. do not teach treating occult brain metastasis. This deficiency is made up for in the teachings of Fidler, et al.

Fidler, et al. teach melanoma metastasizes to the brain in 40-60% of patients (page 387).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have treated melanoma metastasis in the brain using the baculovirus composition of the Lu, et al. as taught by Fidler, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the baculovirus cell composition of Lu, et al. for brain metastasis because Fidler, et al. teach that melanoma frequently metastasizes to the brain. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the treatment method of Lu, et al. for treatment of brain metastasis.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 1-4, 7-14, and 16-18 are rejected under 35 U.S.C. 103(a) as being obvious over Lu, et al. (International Journal of Cancer 2002, Vol. 100 pages 480-485)

in view of Fidler, et al. (Cancer and Metastasis Reviews 1999, Vol. 18, pages 387-400) and further in view of Watts, et al (Cancer Immunology and Immunotherapy 1999, Vol. 47 pages 343-351).

Claims 1-4, 7, 8, and 10-14 have been described supra.

Claims 9 and 16-18 are drawn to a method for treating occult metastasis by administering to a subject a composition comprising an immunomodulatory peptide and a baculovirus-insect cell preparation comprising three administrations of the composition where in the composition further comprises a tumor antigen.

Lu et al. has been described supra. Lu, et al. do not teach treating occult brain metastasis with three doses of the baculovirus preparation. These deficiencies are made up for in the teachings of Fidler, et al and Watts, et al.

Fidler, et al. has been described supra.

Watts, et al. teach a baculovirus expressed SV-40 T-Ag preparation administered in three injections at approximately 14-day intervals (page 344, 2nd column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have treated melanoma metastasis in the brain using the baculovirus composition of the Lu, et al. as taught by Fidler, et al with the dosage schedule of Watts, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the baculovirus cell composition of Lu, et al. for brain metastasis because Fidler, et al. teach that melanoma frequently metastasizes to the brain.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the treatment method of Lu, et al. with the dosage regimen of Watts, et al. for treatment of brain metastasis.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

15. Claims 1 and 22 are rejected under 35 U.S.C. 103(a) as being obvious over Lu, et al. (International Journal of Cancer 2002, Vol. 100 pages 480-485) in view of Fidler, et al. (Cancer and Metastasis Reviews 1999, Vol. 18, pages 387-400) and further in view of Markesbery, et al. (Archives of Neurology 1978, Vol. 35 No. 11 pages 754-756, abstract only).

Claim 1 has been described supra.

Claim 22 is drawn to a method for treating occult metastasis by administering to a subject a composition comprising an immunomodulatory peptide and a baculovirus-insect cell preparation wherein the subject has previously received cancer therapy.

Lu et al. has been described supra. Lu, et al. do not teach treating occult brain metastasis in a subject who has previously received cancer therapy. These deficiencies are made up for in the teachings of Fidler, et al and Markesbery, et al.

Fidler, et al. has been described supra.

Markesbery, et al. teach that some therapy in intracranial metastatic neoplasms is better than no therapy, the prognosis of survival of patients with a single metastatic lesion was only slightly better than that of patients with multiple metastatic lesions.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have treated melanoma metastasis in the brain using the baculovirus composition of the Lu, et al. as taught by Fidler, et al. after a previous cancer therapy as evidenced by Markesbery, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the baculovirus cell composition of Lu, et al. for brain metastasis because Fidler, et al. teach that melanoma frequently metastasizes to the brain and Markesbery, et al. teach that the prognosis for metastatic lesions is poor. Therefore, one of ordinary skill in the art would have been motivated to use additional treatments to improve the prognosis of a subject with brain metastasis.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the treatment method of Lu, et al. for treatment of brain metastasis.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

December 18, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER